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A Child With Radius Aplasia, Cleft of Lip and Palate, Microcephaly, and Unusual Chromosome Findings

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Abstract

We report a child with malformation syndrome of microcephaly, asymmetrical radius aplasia, and cleft of lip and palate, who was mosaic for a chromosome marker and/or ring of unknown origin. In view of the reported cases of limb deficiency with chromosome abnormalities and the unlikelihood that the patient has a recognized genetic syndrome, the cause of the patient's syndrome may well be the extra chromosomal material.

Keywords

multiple congenital anomalies (MCA) syndrome; radius aplasia; microcephaly; cleft lip and palate; aneuploidy; ring chromosome; marker chromosome

INTRODUCTION

We report a patient with multiple congenital anomalies and a chromosome abnormality that poses a diagnostic difficulty. Our patient had a small head, normal birth length, asymmetric shortness of the upper limbs, normal length of lower limbs with mild foot deformities, and cleft of lip and palate; she was mosaic for a chromosome marker and/or ring of unknown origin. To our knowledge no other patient has been reported with these anomalies and a similar chromosome abnormality.

Report of Patient

This white female was born at term to a 20-year-old primagravida mother after an uncomplicated pregnancy. The labor was prolonged and meconium-stained amniotic fluid was noted at delivery. Birth weight, length and occipitofrontal circumference (OFC) were 2.85 kg (10th centile), 49.5 cm (40th centile), and 31 cm (–2.5 SD), respectively. At birth, multiple anomalies were noted, including right cleft lip and cleft palate, bilateral phocomelia, and bilateral foot deformity (Fig. 1). Additional anomalies included ridging of the lambdoid sutures, ocular hypertelorism, small, apparently low-set ears (both 3.0 cm long), malformed right ear, anteriorly displaced parietal hair whorl, short forehead, webbed

neck, heart murmur, enlarged clitoris, prominent labia majora, and single umbilical artery. Asymmetric shortness of both upper limbs was more severe on the left; the infant had a bilateral club-hand deformity, absent thumbs, three fingers on left with absent second digit and a small rudimentary extra digit from the first digit, hypoplastic finger and toenails, hypoplastic terminal phalanges of the fifth fingers, and an immobile right elbow joint. On the right the distance from wrist to elbow was 3.5 cm and from elbow to shoulder was 7 cm. On the left the distance from wrist to apparent elbow was 0.5 cm and from the apparent elbow to the shoulder was 3.5 cm. The child had no head control. Reflexes were 1+ and equal in the lower limbs; muscle tone was equal on both sides. Suck was good and there were no focal neurological signs. Radiographs showed absence of the radii, a small remnant of left humerus, absence of left ulna, presence of right humerus, a globular heart, normal cervical vertebrae, and normal long bones of the lower limbs. A computerized tomographic scan of the head was normal. Skull radiographs showed open sutures and microcephaly. Transposition of the great vessels and a ventricular septal defect were demonstrated by cardiac catheterization. There was no family history of consanguinity or similarly affected relatives.

On ophthalmologic examination the right disc was slightly smaller than the left. An electroencephalographic pattern was diffusely slow for age. No lateralizing, localizing, or epileptiform activities were noted. A neurogenic bladder was noted by the urological consultant. Dermatoglyphic findings included absent thenar creases and axial triradius, bilateral simian crease, single flexion crease of "little" finger on left hand, and hypoplastic or absent flexion creases on several other digits. One fingertip arch was noted. There was one distal loop on the left hand and a palmar interdigital IV distal loop on the right hand. A fibular arch on the right hallux and bilateral plantar interdigital II distal loops were noted.

Leukocytes were cultured for chromosome studies in Gibco Medium 5A. Colcernid treatment (Ciba:0.6 $\mu\text{g}/\text{ml}$) was for 40 min. The patient was found to be mosaic with the majority of the cells containing a very small ring or marker. Fifty-one cells were examined and four cells were 46,XX, two were 47,XX and contained a definite ring chromosome, thirty-nine cells were 47,XX+mar, which varied in morphology and could represent a ring, and six cells had forty-eight chromosomes with two markers and/or rings (Fig. 1). The small centric marker, approximately the size of a G chromosome, was lightly stained but its origin could not be delineated. The ring contained a dark centromeric heterochromatic region as identified in early metaphase preparations but the rest of the chromosome was lightly stained. It appeared to be dumbbell shaped, as a minute fragment or as a definite ring. The centromere splitting or heterochromatin separation phenomenon observed in patients with Roberts syndrome was not observed in our patient [German, 1979; Qazi et al, 1979; Tomkins, Hunter, and Roberts, 1979; Louie and German, 1981]. Parental chromosomes were normal.

The patient died at 1 mo from cardiopulmonary arrest secondary to severe acute bronchopneumonia, thus precluding further characterization of the ring and marker chromosome. An autopsy confirmed the defects listed above and microencephaly. Brain sections were reviewed by Dr. G. Azzarelli, who reported them normal. Ovarian sections were reviewed by Dr. Thomas Ulbright and Dr. Laurence Roth. The ovaries were normal.

They contained numerous primordial follicles but no Graafian follicles. The kidney sections were also unremarkable.

DISCUSSION

This patient had a multiple congenital anomalies (MCA) syndrome of microcephaly, cleft of lip and palate, radius aplasia, and congenital heart defect, and died in early infancy. A marker chromosome, whose origin could not be defined, was present in most cells. The questions that arise are 1) is this a known syndrome with incidental mosaicism for the marker chromosome or 2) is the marker responsible for an aneuploidy syndrome? In attempting to answer the first question, we considered disorders that may produce a similar picture. These include the Roberts/SC phocomelia [Herrmann et al, 1969; Lenz, Marquardt, and Weicker, 1974; Freeman et al, 1974; Herrmann and Opitz, 1977], Holt-Oram [Kaufman et al, 1979], and TAR (thrombocytopenia, radial aplasia) [Smith, 1976] syndromes. Our patient resembles more closely the Roberts/SC phocomelia syndrome but differs in the following respects: normal birth length, asymmetric limb defect, no eye anomalies, no centromere splitting phenomenon, and presence of chromosome markers. It is unlikely that our patient has the Holt-Oram syndrome since cleft of lip and palate is not a manifestation of that condition. Absence of the thumbs and normal platelets seen in our patient are not characteristic of the TAR syndrome.

The second question is more difficult to answer because we were unable to determine the origin of the marker chromosome. The marker chromosome varied in morphology and most likely represented a ring chromosome that was difficult to resolve because of the small size. Cases have been reported of limb deficiency and chromosome abnormalities (trisomies, translocations, and rings) involving the B, C, D, E, and G groups [Bofinger et al, 1973] but no comparable case report has been found. It is possible that our patient's chromosome markers contain active genetic information and caused her malformation syndrome. It is likely that the result is a previously unrecognized genetic syndrome.

We would be most grateful to receive reports of similar cases.

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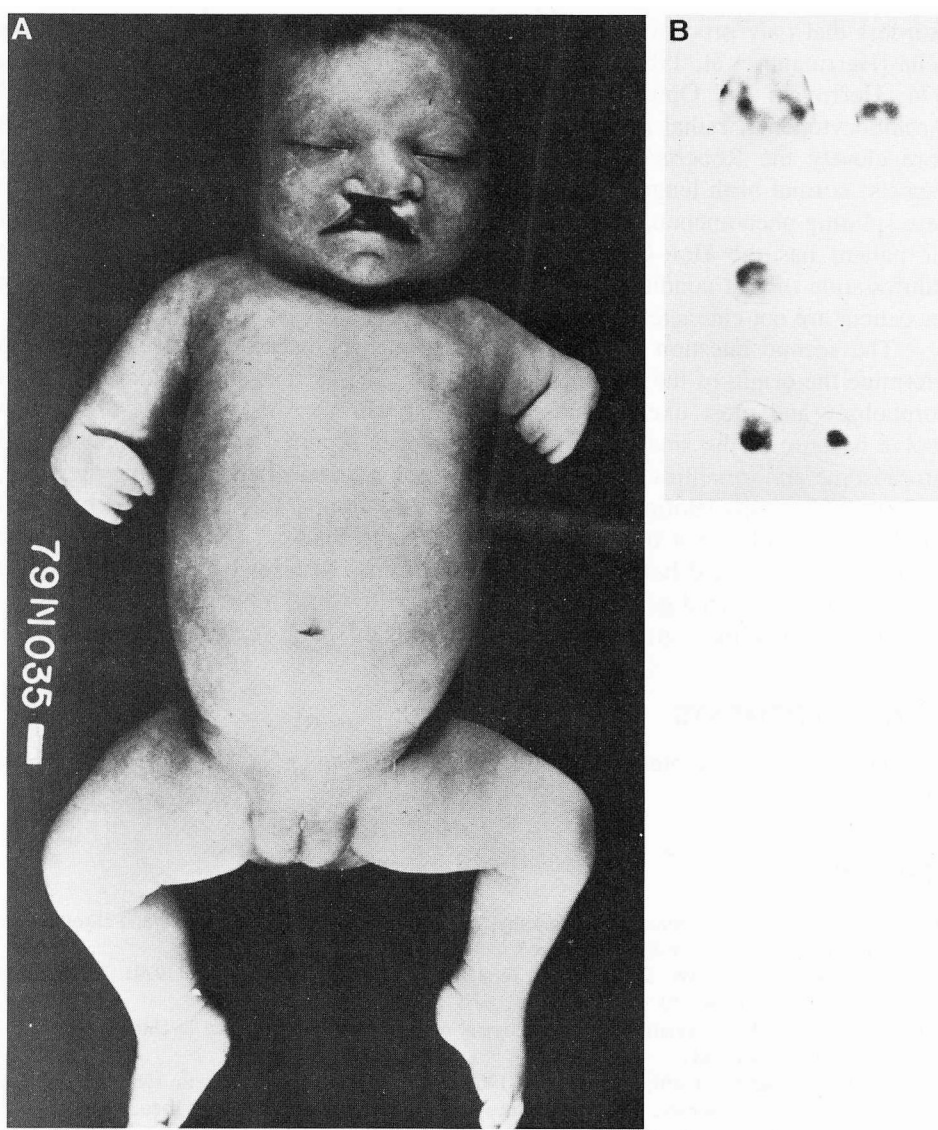


Fig. 1.
(A) Patient at time of death. (B) Selection of chromosome markers and rings from three different cells.